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Restrictive Ventilatory Impairment and Arterial Oxygenation Characterize Rest and Exercise Ventilation in Patients After Fontan Operation

H. Ohuchi,[1] H. Ohashi,[1] H. Takasugi,[1] O. Yamada,[1] T. Yagihara,[2] S. Echigo[1]

[1]Department of Pediatrics, National Cardiovascular Center, 5-7-1, Fujishiro-dai, 565-8565, Suita, Osaka, Japan

[2]Department of Thoracic surgery, National Cardiovascular Center, 5-7-1, Fujishiro-dai, 565-8565, Suita, Osaka, Japan

Abstract. The objective of this study was evaluate the relationships between abnormal pulmonary circulation, lung function, and respiratory response during exercise in Fontan patients. Pulmonary function and cardiopulmonary exercise tests were performed in 101 Fontan patients and 122 controls. A small vital capacity (VC) with a high residual volume-to-total lung capacity ratio and a slight but significant low arterial saturation with hypocapnia were observed in Fontan patients. The number of surgical procedures determined VC. Total cavopulmonary connection, fenestration, higher pulmonary arterial wedge pressure, and smaller VC were independent determinants of low arterial saturation, which was the only determinant of hypocapnia. Arterial saturation decreased during exercise and resting arterial saturation correlated with that at peak exercise. Improvement in dead space ventilation was less in Fontan patients and was independently determined by resting arterial saturation. A steeper minute ventilation–carbon dioxide production slope was determined by resting arterial saturation, arterial carbon dioxide tension, and peak oxygen uptake. In Fontan patients, in addition to dead space ventilation, surgery-related reduced VC, the type of repair, and high pulmonary arterial wedge pressure cause arterial desaturation with subsequent hypocapnia, resulting in accelerated inefficient ventilation at rest and during exercise.

Keywords: Fontan procedure — Hypoxia — Hypocapnia — Exercise — Ventilation

Post-Fontan patients have an abnormal pulmonary circulation, cardiorespiratory response to exercise [6, 7, 12, 20], and impaired pulmonary function [10, 17]. However, their interrelationships, including pulmonary gas exchange or the influence of type of repair, have not been well demonstrated. Although the ventilatory response during exercise characterizes the severity of chronic congestive heart failure [3], it is unclear whether the abnormal ventilatory response characterizes the Fontan patients or stratifies their functional status. Therefore, we analyzed the ventilatory response and pulmonary gas exchange during exercise and compared the results with clinical profiles, including hemodynamics and pulmonary function.

Correspondence to: H. Ohuchi, Physiological Imaging Labratory, A12-404 Mayo Clinic, 200 1 st Street S.W., Rochester, MN 55905, USA. *email:* ouchi.hideo@mayo.edu

Materials and Methods

Patients

Of the 230 patients who underwent the Fontan operation between October 1979 and October 1999 at our institute, 101 of the 195 survivors who had performed exercise and pulmonary function tests were studied (Table 1). Surgical procedures included atriopulmonary connection (APC) in 29 patients and total cavopulmonary connection (TCPC) by intraatrial rerouting either with a polytetrafluorethylene tube in 38 patients or with a heterologous pericardial baffle in 24. TCPC was achieved without cardiopulmonary bypass in 10 patients (Table 1). Fenestration was created at the time of the Fontan operation in 4 patients, in 1 of whom it closed spontaneously, a trivial shunt persisted in 1, and a significant fenestration was demonstrated in the other 2. Patients with ventricular tachycardia who had received a beta blocking agent were excluded from the study. The control group consisted of a cohort of 64 male and 58 female patients aged 5–24 years with a history of Kawasaki disease without stenotic coronary arterial lesions. None of the controls had abnormal findings on physical examination, chest x-ray, electro cardiogram (ECG), two-dimensional echocardiogram, or treadmill exercise test.

Cardiac Catheterization and Ventricular Morphology

In 81 Fontan patients and 42 controls, cardiac catheterization with cineventriculography was performed within 6 months of exercise testing. We measured vascular and chamber pressures. Oxygen consumption was estimated from age, sex, and heart rate data and

Table 1. Clinical characteristics of the study patients[a]

Characteristic	Fontan	Control
Patients (male:female)	101 (43:58)	122(58:64)
Age (years)	13.6 ± 4.6	12.4 ± 4.4
Height (cm)	144 ± 16	147 ± 18
Age at Fontan (years)	6.5 ± 4.6	—
Type of Fontan		—
Atriopulmonary connection	29	
Total cavopulmonary connection	72	
No. of operations	2.5 ± 1.2	—
Follow-up (years)	7.1 ± 3.6	—
Disease		History of KD
Univentricular heart	31	—
Tricuspid atresia	30	—
Double-outlet right ventricle	18	—
Mitral atresia	12	—
Others	10	—
Cardiac function	n = 81	n = 40
Pulmonary artery pressure (mmHg)	11 ± 3	12 ± 3
Pulmonary arterial wedge pressure (rnmHg)	7 ± 3**	6 ± 2
End diastolic volume index (ml/m^2)	78 ± 30	76 ± 16
Ejection fraction of the systemic ventricle (%)	53 ± 12***	72 ± 7
Cardiac index (L/min/m^2)	2.5 ± 0.6***	3.9 ± 0.7

KD, Kawasaki disease.
[a]Values are mean ± SD
**$p < 0.001$ vs. control
***$p < 0.001$ vs. control

cardiac index was measured using the Fick principle with the assumption that right and left pulmonary arterial saturations were equal in patients with a bidirectional Glenn anastomosis because it was clinically difficult to measure a precise distribution of right and left pulmonary blood flow [17].

Ventricular morphology was determined angiographically and patients were subdivided into two groups [17]: (1) a non-left ventricular-type group with either a dominant right ventricle with or without a rudimentary left ventricle (n = 42) or the presence of both right and left ventricles (n = 14) (group non-LV, n = 56), and (2) a dominant left ventricle group with or without a rudimentary right ventricle (group LV, n = 45). The volumes of the right and left ventricles were calculated using Simpson's rule and the area–length method, respectively. For standardization, end diastolic ventricular volume was divided by body surface area (volume index). Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volume (%).

Significant fenestration was seen in two patients, and moderate to severe atrioventricular valve regurgitation was observed in four patients.

Pulmonary Function Tests

In all Fontan patients and 44 controls, we measured vital capacity (VC; L), the percentage forced expiratory volume in 1 second (Spirosift SP-600, Fukuda Denshi, Tokyo), the functional residual capacity (ml), residual volume (ml), total lung capacity (L) (Ellopse-1000 system, Fukuda Denshi), and the diffusion capacity of carbon monoxide of the lung (DLCO, ml/min/mmHg) by a single breath method. VC was also calculated as the percentage of the body height predicted normal value for 44 controls. We calculated the ratio of residual volume to total lung capacity (RV/TLC). Arterial oxygen saturation (SaO_2) in 20 Fontan patients without cardiac catheterization was measured by pulse oxymeter (PULSOX-M2, Teijin, Tokyo) in the outpatient clinic after a supine rest.

Exercise Protocol

All patients exercised on a treadmill (Q-5000 system, Quinton, Seattle, WA, USA). After a 3-minute warm-up (1.5 km/min and 0% grade), treadmill speed and grade were increased at 30-second intervals [15]. All patients were exercised to the end of their tolerance.

Measurements. A 12-lead ECG was recorded throughout the exercise test. Ventilation was measured by a breath-by-breath method. Subjects breathed through a fitted mask and a hot wire anemometer (Riko AS500, Minato Medical Science, Osaka, Japan) measured inspired and expired flow continuously. The partial pressures of oxygen and carbon dioxide were measured continuously at the mouth with a mass spectrometer (MG-300, Perkin–Elmer, St Louis, MO, USA). The respiratory rate (breaths/min), tidal volume (L), minute ventilation (VE; L/min), oxygen uptake (VO_2; ml/min), carbon dioxide production (ml/min), respiratory gas exchange ratio, and the oxygen and carbon dioxide ventilatory equivalents were computed in real time. Peak VO_2 was also expressed as a percentage of predicted normal values. Ventilatory anaerobic threshold was defined by Wasserman's criteria and/or determined by the V-slope method [1, 23] Normal data were also obtained from 122 controls as described previously [14].

Arterial Blood Gas Analysis. Blood samples were taken from an indwelling 22 G angiocath placed in a radial or brachial artery in 16 Fontan patients (APC = 6; TCPC = 10) and 15 controls. Samples were taken at rest, 3 minutes after warm-up walking began, at AT, and at peak exercise and stored on ice (< 20 min) until analyzed for pH, bicarbonate, and arterial partial pressures of oxygen and carbon dioxide (PaO_2 and $PaCO_2$; ABL3 blood gas analyzer, Radiometer, Copenhagen, Denmark). Arterial blood lactate concentration (mmol/L) was measured by an enzyme electrode.

Calculations. The physiologic dead space/tidal volume ratio (V_D/V_T) was calculated using Enghoff's modification of the Bohr equation with $PaCO_2$ [8], The ratio of change in VE to that in carbon dioxide production from warm-up to peak exercise (VE/VCO_2 slope) was also calculated as an index of ventilatory acceleration and efficiency.

Informed Consent

Informed consent was obtained from each subject and his or her parents. This protocol was in agreement with the guidelines of the ethics committee of the National Cardiovascular Center, Osaka, Japan.

Statistical Analysis

The difference in cardiopulmonary function was evaluated using one-way analysis of variance with Scheffe's post hoc test. Simple regression analysis was used to determine correlations between continuous parameters obtained. To detect independent predictors that determined ventilation, pulmonary gas exchange, and aerobic exercise capacity by stepwise multivariate linear regression analysis, we used 11 indices of patients' background; [ages at exercise test and Fontan operation, follow-up period, number of surgical procedures, ventricular morphology (left ventricular type or not), type of Fontan operation (APC or TCPC, with or without a fenestration), with or without a history of pulmonary artery banding, with or without a previous Glenn anastomosis, with or without a significant atrioventricular valve regurgitation, and with or without a diuretic medication], hemodynamic parameters (mean pulmonary arterial, wedge and ventricular end-diastolic pressures, volume index, ejection fraction, and cardiac index), and pulmonary parameters (VC, RC/TLC, percentage forced expiratory volume in 1 second, DLCO, SaO_2, and resting $PaCO_2$ and V_D/V_T). Data are expressed as the mean ± SD. A p value < 0.05 was considered statistically significant.

Results

Hemodynamics

Pulmonary arterial wedge pressure was higher and ejection fraction and cardiac index were lower in Fontan patients than in controls (Table 1).

Pulmonary Function

Although an obstructive ventilator impairment was not observed, total lung capacity, VC, and functional residual capacity were lower and the RV/TLC was higher in Fontan patients than in controls. Because there was no difference in residual volume between Fontan patients and controls, a high RV/TLC indicated "air trapping" in the lung after the Fontan operation (Table 2). Lower percentage predicted VC and higher RV/TLC were independently determined by the number of surgical procedures ($p < 0.001$). Older age at exercise test and large ventricular volume index independently determined a higher RV/TLC ($p < 0.001$). DLCO was lower in Fontan patients and a lower DLCO was determined by an older age at exercise test and a smaller VC ($p < 0.001$ for both).

Resting SaO_2 was lower in Fontan patients and a lower SaO_2 was determined independently by the procedures of TCPC and fenestration ($p < 0.01$ for both), higher pulmonary arterial wedge pressure ($p < 0.001$), and smaller VC ($p < 0.05$).

Exercise capacity

Gas exchange ratio at peak exercise exceeded 1.10 in all groups. Exercise duration, time of the AT, and peak VO_2 and its percentage for controls were markedly lower in Fontan patients than in controls (Table 3).

Pulmonary gas exchange, Blood lactate, and Arterial Gas Analysis during Exercise

Blood Lactate. Blood lactate tended to be higher in Fontan patients ($n = 7$) from warm-up to the AT exercise level, but the peak value was lower compared to that of controls ($n = 8$) ($p < 0.01$). When the change in blood lactate was plotted against that in VO_2, the change in lactate was greater in Fontan patients (Fig. 1a).

pH, Bicarbonate. PH was higher in Fontan patients ($n = 16$) than in controls ($n = 15$) throughout the test ($p < 0.05$–0.01), and bicarbonate from rest to the AT exercise level was lower in Fontan patients than in controls ($p < 0.05$). When the pH and bicarbonate changes were plotted against those in VO_2, the changes were greater in Fontan patients (Figs 1a and 1c).

PaO_2. PaO_2 was lower in Fontan patients ($n = 16$) than in controls ($n = 15$) throughout the test ($p < 0.0001$). PaO_2 was lower in TCPC patients than in APC patients ($p < 0.01$) and decreased during exercise ($p < 0.05$) (Fig. 2a).

SaO_2. SaO_2throughout the exercise test was lower in Fontan patients ($p < 0.1$, $n = 16$) and its decline tended be lower in Fontan patients than in con-

Table 2. Comparison of pulmonary function between Fontan and control groups[a]

	Fontan	*n*	Control	*n*
VC(L)	2.01 ± 0.80***	101	3.13 ± 1.01	44
% predicted VC	80 ± 20***	101	100 ± 15	44
Forced expiratory volume in 1 sec (%)	91 ± 7*	101	88 ± 5	44
Total lung capacity (L)	2.67 ± 0.94***	97	3.72 ± 1.15	43
Residual volume (L)	0.84 ± 0.35	97	0.84 ± 0.44	43
Functional residual capacity (L)	1.25 ± 0.45**	97	1.54 ± 0.57	43
RV/TLC (%)	32 ± 8***	97	22 ± 8	43
DLCO (ml/min/mmHg)	13.5 ± 5.5***	87	21.7 ± 5.8	34
SaO_2 at rest(%)	94 ±3***	101	96 ± 2	44
VE at rest (L/min/kg)	0.27 ± 0.07#	101	0.26 ± 0.09	122
$PaCO_2$ at rest (mmHg)	36 ± 2***	101	40 ± 1	122
V_D/V_T at rest	0.44 ± 0.06	101	0.44 ± 0.06	122

[a]Values are mean ± SD.
#$p < 0.1$ vs control.
*$p < 0.05$ vs control.
**$p < 0.01$ vs control.
***$p < 0.001$ vs control.
VC, vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusion capacity of carbon monoxide of the lung; VE, minute ventilation; SaO_2, arterial oxygen saturation; $PaCO_2$, arterial carbon dioxide tension; V_D/V_T, dead space/tidal volume ratio.

trols($p < 0.001$). Resting SaO_2 correlated well with that at peak exercise ($r = 0.80$, $p < 0.001$) and tended to correlate with its decrease from rest to peak exercise ($r = 0.43$, $p < 0.1$).

Arterial to End-Tidal Oxygen and Carbon Dioxide Tension Differences. End-tidal to PaO_2 difference was greater in Fontan patients than in controls throughout the study ($p < 0.001$) and it was greater in TCPC patients than in APC patients ($p < 0.05$). Although the arterial to end-tidal carbon dioxide tension difference was greater in Fontan patients ($p < 0.05$–0.001), no difference was observed between groups of APC and TCPC. Because a tight correlation between end-tidal and arterial carbon dioxide tensions in Fontan and control subjects ($n = 31$) was demonstrated at rest, warm-up, AT, and peak exercise ($PaCO_2 = 16.7 + 0.62 \cdot x$, $16.6 + 0.57 \cdot x$, $17.6 + 0.53 \cdot x$, and $17.0 + 0.52 \cdot x$, respectively, where x is end-tidal carbon dioxide tension; $r = 0.84$–0.91, $p < 0.0001$), it was possible to estimate $PaCO_2$ from end-tidal carbon dioxide tension and apply these equations to the other patients and controls without an arterial gas analysis to calculate V_D/V_T.

$PaCO_2$. Resting $PaCO_2$ was lower in Fontan patients than in controls and was determined by only SaO_2 ($p < 0.001$) when resting ventilatory equivalent for carbon dioxide production was excluded from the multivariate analysis. There was no difference in change in $PaCO_2$ from rest to peak exercise between Fontan patients and controls; a lower $PaCO_2$ persisted throughout exercise in the Fontan patients ($p < 0.001$; Fig. 2b).

Respiratory Pattern

Resting respiratory rate was faster in Fontan patients (Table 3), and a smaller VC ($p < 0.001$) and lower $PaCO_2$ ($p < 0.01$) independently determined the faster respiratory rate. Tidal volume tended to be smaller in Fontan patients, and the smaller tidal volume was independently determined by a smaller VC ($p < 0.001$). VE per body weight tended to be greater in Fontan patients and a lower $PaCO_2$, smaller VC, younger age ($p < 0.001$ for all) and higher RV/TLC ($p < 0.05$) independently determined resting VE.

Respiratory rate, tidal volume, and VE at peak exercise and their changes from rest to exercise were smaller in Fontan patients than in controls ($p < 0.001$). However, ratios of change in respiratory rate to that in VE from both rest to the AT and AT to peak exercise were higher and a ratio of change in tidal volume from rest to the AT level was smaller in Fontan patients than in controls ($p < 0.01$–0.001) (Table 3). The higher former ratio and lower latter ratios were independently determined by a smaller VC ($p < 0.001$). Relationships between respiratory rate, tidal volume, and VE are illustrated in Fig. 3. Diffusion capacity and the V_D/V_T also independently determined respiratory rate increase from rest to the AT exercise ($p < 0.05$); however, because these two indices were independently determined by VC, VC

Table 3. Exercise variables of the study patients[a]

Variable	Fontan	Control
Exercise time (min)	6.3 ± 1.5***	9.7 ± 1.3
AT appearance (min)	2.3 ± 0.8***	3.0 ± 1.1
PeakVO_2 (ml/kg/min)	24.8 ± 4.9***	44.2 ± 7.4
Peak VCO_2 (% of normal)	54 ± 10***	100 ± 13
Ventilation		
Rest		
Respiratory rate (breaths/min)	22 ± 5**	20 ± 4
Tidal volume (L)	0.46 ± 0.16#	0.50 ± 0.15
VE (L/min/kg)	0.27 ± 0.07#	0.25 ± 0.08
$PaCO_2$(mmHg)	36 ± 2***	40 ± 2
PaO_2 (mmHg)	77 ± 12***	110 ± 4
V_D/V_T	0.45 ± 0.06	0.44 ± 0.06
VE/VCO_2	56 ± 8***	47 ± 5
SaO_2 (%)	94 ± 3***	96 ± 2
Peak		
Respiratory rate (breaths/min)	49 ± 11***	55 ± 12
Tidal volume (L)	0.97 ± 0.38***	1.27 ± 0.47
VE (L/min/kg)	1.26 ± 0.29***	1.69 ± 0.37
$PaCO_2$ (mmHg)	34 ± 3***	38 ± 3
PaO_2 (mmHg)	72 ± 13***	101 ± 11
V_D/V_T	0.43 ± 0.06***	0.36 ± 0.06
VE/VCO_2	47 ± 10***	35 ± 6
SaO_2 (%)	92 ± 4***	97 ± 1
Change from rest to peak		
Respiratory rate (breaths/min)	27 ± 9***	35 ± 11
Tidal volume (L)	0.51 ± 0.25***	0.77 ± 0.38
VE (L/min/kg)	0.99 ± 0.25***	1.43 ± 0.32
$PaCO_2$ (mmHg)	−2 ± 2	−2 ± 3
PaO_2 (mmHg)	−5 ± 8	−10 ± 11
V_D/V_T	−0.02 ± 0.05***	−0.06 ± 0.07
VE/CO_2	−9 ± 8**	−12 ± 7
SaO_2(%)	−3 ± 3#	−1 ± 1
Ventilatory pattern		
Rest to AT		
Increase in respiratory rate to that in VE ratio	0.98 ± 0.57***	0.72 ± 0.41
Increase in tidal volume to that in VE ratio	25 ± 59**	67 ± 115
AT to peak		
Increase in respiratory rate to that in VE ratio	0.76 ± 0.38**	0.63 ± 0.32
Increase in tidal volume to that in VE ratio	11 ± 6#	10 ± 5
Ventilatory efficiency		
VE/VCO_2 slope	43 ± 12***	33 ± 6

AT, anaerobic threshold; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen saturation; SaO_2, arterial oxygen; V_D/V_T, dead space to tidal volume ratio; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide.
[a]Values are mean ± SD.
#$p < 0.1$ vs control.
**$p < 0.01$vs control.
*** $p < 0.001$ vs control.

was the most important and powerful determinant of respiratory pattern at rest and during exercise.

Ventilatory Efficiency

Although there was no difference in resting V_D/V_T between Fontan patients and controls, the decline (improvement) in V_D/V_T from warm-up to peak exercise was smaller ($p < 0.001$) in Fontan patients, and a lower $PaCO_2$ as well as a lower V_D/V_T independently determined this improvement ($p < 0.001$). Resting ventilatory equivalent for CO_2 and VE/VCO_2 slope were markedly higher in Fontan patients than in controls (Table 3). Higher resting ventilatory equivalent for carbon dioxide was independently determined by a lower $PaCO_2$ and a higher RV/TLC ($p < 0.001$), and a higher VE/VCO_2 slope was inde-

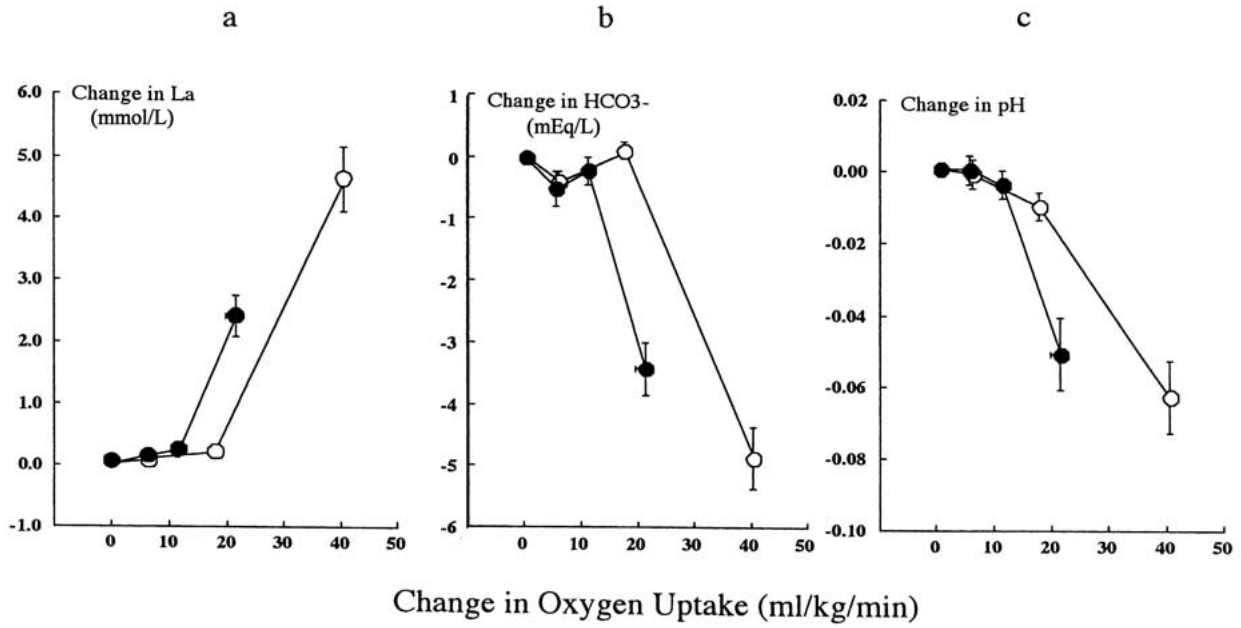

Fig. 1. Changes in lactate concentration (*La*);(**a**), bicarbonate (HCO_3^-) (**b**), and pH (**c**) during exercise.

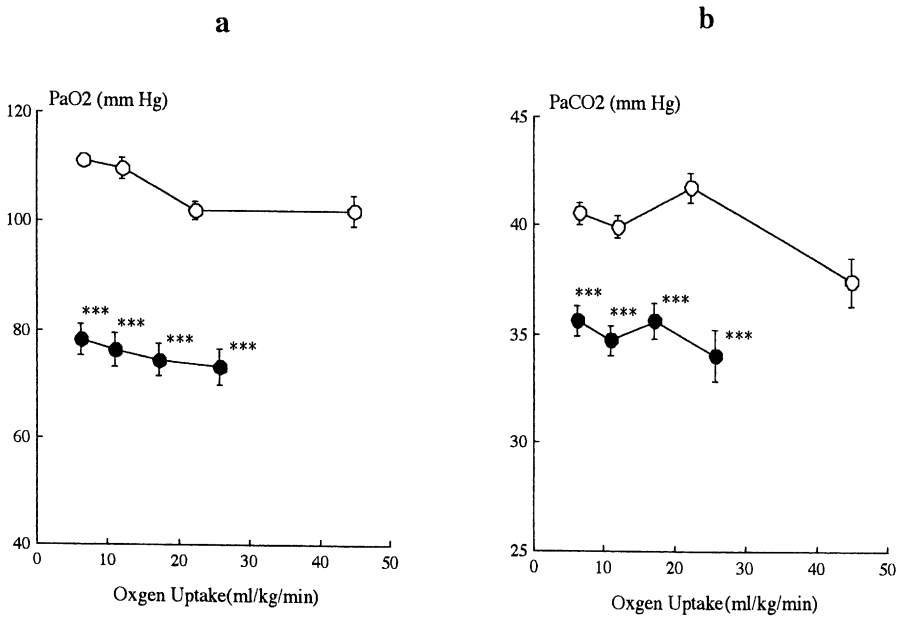

Fig. 2. Changes in arterial oxygen tension (PaO_2) (**a**) and carbon dioxide tension ($PaCO_2$) (**b**) during exercise.***$p < 0.001$

pendently determined by a lower SaO_2 ($p < 0.05$) and a lower $PaCO_2$ ($p < 0.001$). Relationships between SaO_2, $PaCO_2$, and the VE/VCO_2 slope are illustrated in Fig. 4. Thus, $PaCO_2$ was the most important and powerful determinant of ventilatory efficiency at rest and during exercise.

Determinants of Aerobic Exercise Capacity

According to a multivariate analysis using patients' background, hemodynamics, and pulmonary variables, lower percentage predicted peak VO_2 was independently associated with older age at exercise

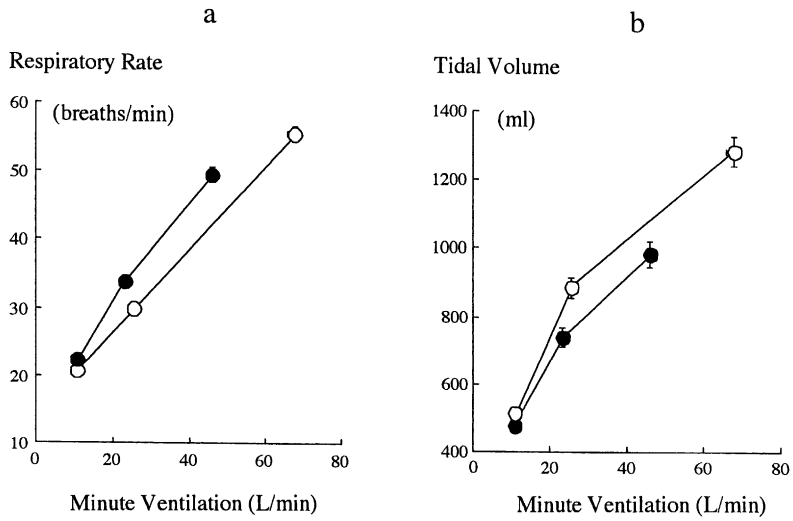

Fig. 3. Relationships between minute ventilation and respiratory rate (**a**) and tidal volume (**b**) during exercise comparing Fontan patients (*solid circles*) and controls (*open circles*).

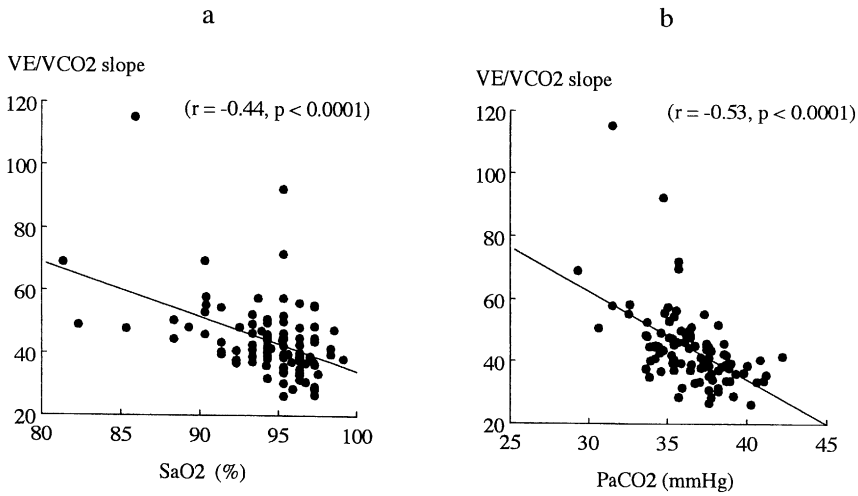

Fig. 4. Relationships between the ratio of change in minute ventilation to that in carbon dioxide production from warm-up to peak exercise (*VE/VCO_2 slope*) and resting arterial saturation (SaO_2) (**a**) and carbon dioxide tension ($PaCO_2$) (**b**).

test ($p < 0.001$), non-left ventricular type ventricle patients ($p < 0.01$), higher RV/TLC ($p < 0.01$), and lower $PaCO_2$ ($p < 0.001$).

Discussion

Our major findings are that after Fontan operation, (1) in addition to TCPC and a fenestration, high pulmonary arterial wedge pressure and surgery-related small VC result in a slight but significant hypoxia that causes significant resting hypocapnia; (2) this secondary resting hypocapnia is an important and powerful determinant of subsequent continuing hypocapnia and accelerated low-efficient ventilation during exercise; and (3) the respiratory pattern is determined only by surgery-related vital capacity and not by the impaired hemodynamics.

Accelerated Low-Efficient Ventilation

The current study demonstrates for the first time that in Fontan patients a slight but significant desaturation is the primary cause of abnormal ventilation at rest and during exercise.

In addition to the high sensitivity of the chemoreceptor to PaO_2 in the carotid body [4], because hypocapnia in cyanotic congenital heart disease has

been demonstrated by several investigators [9], the secondary hypocapnia demonstrated in our study is not surprising.

Right-to-left shunting, ventilation–perfusion mismatch in the lung, and diffusion capacity are the major factors that cause arterial hypoxia. In the usual TCPC, and also fenestration, coronary and systemic venous return(s) through small channels from great veins drains to the systemic atrium and there is often slight leakage through the intraatrial rerouting baffle—both causes of mild hypoxia. The greater difference in the end-tidal to arterial oxygen tension difference in TCPC patients compared to APC patients indicates that the significant difference in SaO_2 between the two groups is due to intra cardiac right-to-left shunting. Because a small VC results from repeated palliative surgeries, the ventilation–perfusion mismatch resulting in hypoxia can be caused by uneven lung inflation (probably together with uneven pulmonary arterial resistance) due to adhesions after surgeries. Because high pulmonary arterial wedge pressure may be a result of both ventricular and atrioventricular valve functions and abnormal intrapulmonary capillary circumstances, the pulmonary circulation may be easily disturbed, leading to ventilation–perfusion mismatch in the lung. In contrast, diffusion capacity is independently determined by VC; therefore, the lower diffusion capacity is not a primary factor in their hypoxia.

Although a high resting ventilatory equivalent for CO_2 inversely correlated well with resting SaO_2 ($r = -0.43$, $p < 0.0001$), because the lower $PaCO_2$ was a secondary phenomenon caused by hypoxia and based on the equation, $VE = 863 \cdot VCO_2/PaCO_2 (1 - V_D/V_T)$, where VCO_2 is a carbon dioxide production, a high ventilatory equivalent for CO_2 is not a cause but a result of hypoxia.

SaO_2 decline during exercise may represent worsening of the ventilation–perfusion mismatch in the lung [10]. However, the tight correlation between resting and peak SaO_2 values implies that factors that determine right-to-left shunting at rest also have a significant influence on progressive hypoxia during exercise [7].

Greater V_D/V_T during exercise has been identified as an important cause of accelerated ventilation in Fontan patients [19]. Although the decline in V_D/V_T is small, it is independently determined by the resting $PaCO_2$ as well as resting V_D/V_T. Moreover, VE/VCO_2 slope is independently determined by resting $PaCO_2$ and SaO_2. Oren et al. [18] demonstrated that $PaCO_2$ during exercise remains at the preexercise level. Based on the alveolar equation described, previously, together with a small V_D/V_T reduction, this mechanism may be very important in explaining how the resting desaturation with subsequent lower $PaCO_2$ has a great impact on accelerated inefficient ventilation during exercise in Fontan patients.

Buffering an accumulating blood lactate by the bicarbonate begins above the AT exercise and produces additional CO_2 production [23]. Influx of carbon dioxide into the lung is an important stimulus to ventilation [22]; therefore, the early appearance of the AT is certainly responsible for accelerated ventilation at a given workload in Fontan patients [24].

Central sensitivity to CO_2 is associated with excess ventilation in heart failure patients [11]. This mechanism may be operative because Fontan patients have similar characteristics as those of heart failure patients (i.e., low cardiac output and exercise capacity and sympathetic activation) [16], although the contribution of this mechanism is unclear in our study. The carotid body sensitivity to PaO_2 is also augmented in heart failure patients [2]. Because an inverse correlation between arterial baroreceptor sensitivity and the chemosensitivity exists in humans [21], chemosensitivity may be augmented in Fontan patients with severely depressed arterial baroreflex sensitivity [13]. Therefore, a high chemosensitivity in addition to mild hypoxia may be another explanation for the accelerated ventilation at rest and during exercise.

Rapid and Shallow Respiration

In Fontan patients, rapid and shallow respiration, as observed in patients with congestive heart failure [5], is determined by a small VC caused by repeated surgical procedures. Therefore, the respiratory pattern (respiratory rate and tidal volume) during exercise does not stratify the hemodynamics of the Fontan circulation.

Impact of Ventilatory Impairment on Aerobic Exercise Capacity

In addition to age at exercise test and ventricular morphology [7, 17], because a lower $PaCO_2$ and higher RV/TLC are associated with lower aerobic capacity, a lower $PaCO_2$ caused by the abnormalities linked to hypoxia may be a sensitive marker of overall cardiopulmonary status. Surgical-related significant chest wall deformity as well as adhesions of the lung may restrict the mobility of the chest wall and the lung. Moreover, a large ventricular volume may also reduce lung mobility. Thus, a high RV/TLC may indicate a reduced mechanical mobility of the lung system, resulting in air trapping, and may also limit aerobic exercise capacity.

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